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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,944	MARKS ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/18/05 & 11/17/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6 and 22-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/05/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 17, 2005 has been entered.

2. Claims 3-6 and 22-28 are pending.

Claims 22-28 have been added.

Claims 19-21 have been canceled.

Claims 3 and 5 have been amended.

Claims 3-6 and 22-28 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Objection

Specification

4. The disclosure is objected to because of the following informalities:

(a) the last sentence of the caption for Figure 3A on page 10, line 24 is missing a period, hence it is not clear what other text is missing; and

(b) page 31, line 17 cites "rapamysin" instead of "rapamycin". Correction is required.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

5. The rejection of claims 19-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' cancellation of the claims.

Claim Rejections - 35 USC § 102

6. The rejection of claims 3-6 under 35 U.S.C. 102(b) as being anticipated by WO 99/65939/ IDS reference from Paper number 8 (23 December 1999) is withdraw in light of the claim amendments. Claims 19-21 have been cancelled.

7. The rejection of claims 3-6 under 35 U.S.C. 102(b) as being anticipated by WO 99/03508/ IDS reference from Paper number 8 (28 January 1999) is withdrawn in light of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 103

8. The rejection of claims 3-6 under 35 U.S.C. 103(a) as being unpatentable over WO 99/03508/ IDS reference from Paper number 8 (28 January 1999), and further in

view of WO 99/65939/ IDS reference from Paper number 8 (23 December 1999) is withdrawn. Claims 19-21 have been cancelled.

Maintained Rejections and New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. Claims 3-6 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Applicants have amended claims 3 and 5 and added new claims 23 and 25 to include limitations reading on the administration of a compound to a subject at least 4mg/day of a compound per kg of the subject's body weight and the administration of rapamycin to a subject at least 4mg/day or 9mg/day of a compound per kg of the subject's body weight. Applicants points out several pages and line numbers that alleged support these amendments and new claims, see page 4 of Remarks submitted August 18, 2005, second paragraph. The Examiner has reviewed all listed pages and lines and does not find adequate support for the new limitations. For instance, page 20, lines 26-29; page 24, lines 22-25; and the caption for Figure 3 on page 10, lines 26-29 note rapamycin was administered for example at 9mg/kg/day for 7 days and 4 mg/kg/day for 5 days. However, the claims do not limit the days of administration and

claims 3 and 5 recite administering an arbitrary compound and not rapamycin, as supported in the specification.

New claim 26 contains language wherein an effective amount of C3 exoenzyme is administered to a subject, however the specification supports the administration of either 2 μg/ml or 20 μg/ml of C3 exoenzyme for 16 hours, see specification page 25, lines 26-30. The Examiner has reviewed other passages in the specification that allegedly support claim 26, but does not find this the case, see Remarks, page 4, second paragraph. Applicants should delete the new matter or cite wherein the specification support the claims.

10. The rejection of claims 3-6 and new claims 26-28 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained and made. Claims 19-21 have been cancelled.

Applicants present the legal standard for lack of enablement and aver the compounds listed in the claims are not undefined and uncharacterized, see page 7, last paragraph and bridging paragraph of pages 8 and 9 of the Remarks. Applicants note "...the specification provides at least two examples of compounds that satisfy the properties specified in the instant claims" and "...the claims are not overly broad", see page 11, first full paragraph and page 12, 4th paragraph. Applicants' points of view and arguments have been fully considered, but found unpersuasive.

While Applicants note in their specification the administration of rapamycin and C3 exoenzyme this does not preclude the instant rejection in the context of the broad claims that embrace the arbitrary term, compound. The unpredictability in the art of administering undefined and uncharacterized compounds for the treatment of cardiovascular disease and cancer is still relevant in the instant case. The broad genus of compounds listed in the claimed invention cannot predictably do the same as C3 exoenzyme or rapamycin. In the previous Action the Examiner established that fact with the article on peroxisome proliferators-activated receptor γ (PPAR γ) ligands. The broadly described molecules may not maintain the activities and function as proposed in the specification. In the absence of an established role of the broad chemical compounds in targeted treatment of cancer and cardiovascular diseases it is impossible to predict what if any therapeutic effect the administration of any of these molecules would have in the said methodologies. There is insufficient data or established precedent presented that would lead one of skill in the art to believe that the broadly listed compounds would be able to function as the methodology dictates, i.e. inhibiting tumor metastasis. The analysis established in this Action, as well as previous Actions belies the Examiner's position that there appears to be no nexus between Applicants' broadly claimed method of treating a subject affected with cardiovascular disease and tumor metastasis by administering a broad genus of undefined compounds.

The specification provides insufficient guidance with regard to administering a plethora of compounds, which increase intracellular cyclin-dependent kinase inhibitor p27 activity for the treatment of disorders. The specification also does not present

sufficient working examples, which would provide guidance and significant preponderance of predictability to one skilled in the art the use of the said compounds with a reasonable expectation of success. In view of the unpredictability of the art one of skill in the art would be forced into undue experimentation to practice implementation of the claimed invention.

11. Claims 3, 4, 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 3 and 26 are vague and indefinite because they read on the administration of compounds for treatment of cardiovascular disease, however they do not note if treatment is the elimination of the disease or reduction of symptoms that characterize the disease. Accordingly, the metes and bounds are not clear.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 3, 4 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Poon et al. (J.Clin. Invest. 98(100: 2277-2283, November 1996)/ DS reference, Exhibit 9). Poon discloses the administration of 5mg/kg for 7 days of rapamycin to animals in

the treatment of restinosis after percutaneous transluminal coronary angioplasty and accelerated arteriopathy after cardiac transplantation, see abstract and page 2278, column 2, Explant...section.

14. Claims 3, 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Poston et al. (Circulation 100: 67-74, 1999). Poston discloses the administration of 5mg/kg-1/d-1 of cyclosporine (CSA) and 10mg/kg/d to rats with chronic graft vascular disease (CGVD), see abstract and page 68, column 1, Immunosuppression section.

15. Claims 3, 4 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Gregory et al. (Transplantation 55(6): 1409-1418, June 1993). Gregory discloses the administration rapamycin (RPM) for 6mg/kg/day for 0-7 days to rats with balloon catheter injury to carotid arteries, see abstract.

Claim Rejections - 35 USC § 103

16. Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/03508/ IDS reference from Paper number 8 (published 28 January 1999).

In anticipation of the instant rejection Applicants remind the Examiner the criteria for establishing an obviousness rejection and a prima facie case of obviousness, see Remarks, bridging paragraph of pages 17 and 18. In conclusion, Applicants note that the claims have been amended to recite specific dosages of the compound to be

administered and neither WO document teaches or suggests this element. Applicant's arguments have been fully considered but they are not persuasive.

The WO 99/03508 teaches methods for treating and preventing cardiovascular diseases *in vivo* including restenosis, artherosclerosis and angiogenesis with a mutated p27 or p27 fused with thymidine kinase, see page 4, lines 6-15 and pages 30 and 31, claims 1-16. This WO document also teaches a method for providing a gene composition which expresses p27 in a therapeutically effective amount to a patient with a vascular proliferative disease, such as atherosclerosis, angiogenesis and restenosis, see page 4, lines 7-21; page 10, line 11-page page 12, line 2. The medicaments upregulate p27 activity. Moreover, inherently the increase/enhancement of the cyclin-dependent kinase inhibitor p27 is due to the increase of C3 exoenzyme activity.

WO document 99/03508 does not teach the administration of the cited compounds in the dosages recited in claims 3 and 5. However, the document suggest "[t]he amount of p27 to be administered will depend on the size of the patient and the state to which the diseases has progressed", see page 10, lines 19 and 20; and page 11, lines 1-12. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to begin treatment in an expeditious manner in order to impede further cardiovascular damage and metastasis at the recited dosages in order to further limit comprising the individual's health. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success since dosages of any composition for treatment must be adjusted and optimized. Thus the claimed subject matter is considered obvious over the prior art, absent sufficient factual

evidence to the contrary.

17. Claims 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/65939/ IDS reference from Paper number 8 (published 23 December 1999).

In anticipation of the instant rejection Applicants remind the Examinter the criteria for establishing an obviousness rejection and a prima facie case of obviousness, see Remarks, bridging paragraph of pages 17 and 18. In conclusion, Applicants note that the claims have been amended to recite specific dosages of the compound to be administered and neither WO document teaches or suggests this element. Applicants' arguments and points of view have been carefully considered but found unpersuasive.

This WO document discloses methods for modulating, i.e. enhancing the activity of a p27(Kip1).FKBP-12 complex, see page 9, lines 24 and 25. Consequent to the enhancement of this intracellular cyclin-dependent kinase inhibitor p27 activity there is cell cycle arrest and control of physiological processes such as hyperproliferative disorders, atherosclerosis and cardiac and muscle disease, see page 9, lines 24-32. The role of the cyclin kinase inhibitor p27(Kip1) is clearly implicated in artherosclerosis, tumorigenesis, tumor progression and spread, see page 7, lines 9-11. "p27(Kip1) expression levels correlate with cancer progression since a decrease in p27(Kip1) expression levels significantly correlates with advanced stage, depth of tumor invasion and lymph node metastasis.", see bridging sentence of pages 5 and 6. Tumor spread is art known to be the migration of cancer cells from one site (i.e. part of the body) to another site. The disclosed invention provides a method for treatment or prevention of various diseases and disorders, such as those related to organ transplantation, tumor

spread, autoimmune diseases and atherosclerosis by administration of a therapeutic compound that modulates, i.e. promotes p27(Kip1).FKBP-12, see page 27, lines 10-29; page 33, lines 3-5. The administration of these compounds upregulate p27 activity and thereby alleviates cardiovascular disease, inhibits tumor metastasis and inherently increases C3 exoenzyme activity.

WO document 99/65939 does not teach the administration of the cited compounds in the dosages recited in claims 3 and 5. However, the document suggest "[t]he amount of the Therapeutic...will be effective in the treatment of a particular disorder or condition...and may be determined by standard clinical techniques...", see page 50, lines 31-33. Furthermore, the WO document suggests "[e]ffective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems", see page 51, lines 1-9. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to begin treatment in an expeditious manner in order to impede further cardiovascular damage and metastasis at the recited dosages in order to further limit comprising the individual's health. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success since dosages of any composition for treatment must be adjusted and optimized. Thus the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary.

18. Claims 3, 4, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gregory et al. (Transplantation 55(6): 1409-1418, June 1993). The

teachings of Gregory have been presented in the 102(b) rejection. Gregory does not teach the administration of at least 9mg/day of rapamycin.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to begin treatment in an expeditious manner in order to impede further cardiovascular damage with the administration of at least 9mg/day of RPM in order to further limit comprising the individual's health. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success since dosages of any composition for treatment must be adjusted and optimized, as well as Gregory suggests "...investigating different RPM doses and treatment schedules in an attempt to inhibit intimal thickening after balloon-catheter injury more effectively", see page 1417, column 1, first full paragraph. Thus the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
06 February 2006